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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/617,915	07/10/2003	Jerome James Workman JR.	MLA.026CP	4223

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EXAMINER	
SCHUBERG, LAURA J	
ART UNIT	**PAPER NUMBER**
1657	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/617,915	WORKMAN ET AL.	
	Examiner	Art Unit	
	Laura Schuberg	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,23-42 and 54-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,23-42 and 54-57* is/are rejected.

7)☒ Claim(s) *33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/18/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/18/2007 has been entered.

Claims 19, 23-42, 54-57 are pending and have been examined on the merits.

Response to Arguments

Applicant's arguments filed 08/17/2007 have been fully considered but they are not persuasive.

Applicant argues that one of ordinary skill in the art would not have had a reasonable expectation of success in trying to combine the teachings of Cote with that of Chick to obtain the presently claimed invention. Applicant asserts that Chick does not provide any teaching as to how one might alter the fluorescent reagents or substitute them with other fluorescent reagents so as to allow the reagent to have a size and chemistry that would allow it to diffuse across the cellular membrane of a skin cell to allow monitoring.

This is not found persuasive because, as Applicant states on page 18 line 28 of the specification, "it is well known that specific dyes bind to cellular structures and allow imaging and anatomical/histological studies of intracellular structures". In addition Chick specifically teaches that a variety of modes of placing the reagents in communication with the analytes may be used (column 16 line 37).

Claim Objections

Claim 33 is objected to because of the following informalities: The terms "the" and "a" are both placed in front of the term "skin sensor" in line 2 of the claim. The correct phrasing with regard to antecedent basis would be "a skin sensor".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19, 23-42, 54-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant has added the limitation of "as

compared to the intensity and/or wavelength that is observed in the absence of the metabolite or analyte" in claim 19. There is insufficient support in the disclosure as originally filed for this limitation; thus it is being considered new matter. The disclosure as originally filed only supports comparing the intensity and/or wavelength that is observed using the known stoichiometric relationship between the fluorescence spectrum of the reporter and the metabolite parameter or analyte concentration (page 4 lines 23-25).

An amendment to the claims or the addition of a new claim must be supported by the description of the invention in the application as filed. In re Wright, 866 F.2d 422, 9 USPQ2d 1649 (Fed. Cir. 1989). Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 19, 23-26, 28, 29, 30-36, 38, 39, 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chick et al (US 6,040,194) in view of Cote et al (US 6,485,703 B1) and Walt et al (US 6,377,721 B1).

Independent claims 19 and 33 are drawn to methods of monitoring the concentration of one or more analytes or *in vivo* blood glucose levels respectively. The methods comprise applying a skin sensor composition to a surface of the skin for a predetermined period of time, wherein the composition comprises a reporter dye, wherein the reporter dye exhibits a change in wavelength and/or intensity of fluorescence emission or absorbance in the presence of a metabolite or analyte as compared to the intensity and/or wavelength that is observed in the absence of the metabolite or analyte; causing penetration of the composition to a depth of about 10 μm, wherein said depth corresponds with the bottom of the dead stratum corneum layer, to about 175 μm, wherein said depth corresponds with the top of the dermal layer, into the epidermis; and monitoring a change in **intracellular** concentration of metabolites or analytes by detecting changes in fluorescence emission or absorbance of the reporter dyes using an optical reader, and (claim 33) correlating the change in **intracellular** concentration of the metabolites or analytes with in vivo blood glucose levels. Dependent claims are drawn to the type of stain or dye used, the type of transport technique used, and the minimum wavelength detected being above 450 nm.

Claims 30 and 40 are drawn to the methods of claims 19 and 33 respectively and includes the additional limitations wherein the penetration depth into the epidermis is accomplished by combining the composition with molecular size attachments.

Applicant defines "molecular size attachments" as adducts to the fluorescent moieties of SMMRs to include, but are not limited to structural modifications of fluorescent SMMRs as the additions to the fluorescence structure of: acetoxy methyl esters and several others (page 14 para 167).

Claims 31 and 41 are dependent on claims 19 and 33 respectively and include the additional limitations of the predetermined time period that the skin sensor composition is applied for.

The limitation of the depth in the skin of 10 μm to 175 μm is interpreted to mean the epidermal layer of the skin. In addition, this limitation is interpreted as not excluding the dermal layer of the skin as long as the composition passes through the epidermis first.

Chick teaches an *in vivo* method and sensor for detecting an analyte in an individual qualitatively or quantitatively. The sensor is placed in communication with the bodily fluids and once in place the sensor does not exit the skin of the individual. Once the sensor is in place, it is illuminated with radiation transdermally and the fluorescence reagent associated with the presence of the analyte is measured (column 2 lines 31-50. For in vivo use, the reagents comprising the fluorescence reagent are placed in, on, or under the skin in communication with (e.g. contacting) body fluid containing the analyte of interest (column 16 lines 24-28). This is interpreted to include the epidermis, thus

meeting the limitation for depth in skin of the sensor (claim 19). Wherein glucose is the analyte detected is taught (column 6 lines 35-38) as well as wherein the dye is combined with glucose oxidase and uses an oxidative metabolic pathway to measure glucose levels (column 15 lines 35-47) (claims 33 and 24). BCECF is specifically taught as a suitable pH probe (column 14 line 63), which also meets the limitations for a xanthene dye (as identified by Applicant page 8 para 90 of the specification) (claims 23,25,26,34-36). A variety of modes of placing the reactants in communication with the analyte are taught including tattooing and a transcutaneous patch (column 17 lines 6-12) (claims 29 and 39). This would inherently include formulations such as a solvent or a disposable gel film patch as well as wicking (from the patch) as a form of transport for penetration of the skin (claims 28, 29, 38 and 39). In addition, spectra were collected by exciting fluorescein at 472 nm and scanning the emission from 500-650 nm (column 11 lines 39-41) (claims 32 and 42). Comparison of fluorescence and wavelength to that found in the absence of the analyte is also taught (column 18 lines 5-19).

Chick is silent with regard to intracellular or extracellular concentrations of analytes measured and does not specifically indicate the time period of application. Chick teaches BCECF, but does not specifically teach the use of BCECF with a molecular size attachment.

Cote teaches compositions and methods for analyte detection (abstract). Cote teaches the importance of monitoring both intra- and extra-cellular analytes, particularly intracellular glucose in diabetic patients since the acute problems related to diabetes are correlated to intracellular glucose levels. Too much insulin causes low glucose in

both extracellular and intracellular fluid (insulin shock). Too little insulin, or insulin receptor resistance, causes low glucose intracellularly and high glucose extracellularly. Information may be gained simultaneously by using two particle sizes: one that is small enough for phagocytosis and one that is too large for phagocytosis (column 24 lines 30-67).

Walt teaches that the acetoxymethyl (AM) ester form of BCECF is non-fluorescent in solution, cell membrane permeant and passively enters the cell where, once inside the cell, the lipophilic blocking groups are cleaved by non-specific esterases resulting in an increase in fluorescent intensity. This increase in fluorescent intensity is indicative of the cell viability as a pH indicator (column 16 lines 48-61).

Therefore, it would have been obvious for one of ordinary skill in the art to include monitoring of intracellular concentrations of one or more metabolites in the method of Chick because Cote teaches the importance of monitoring both intra- and extra-cellular analytes, particularly intracellular glucose in diabetic patients since the acute problems related to diabetes are correlated to intracellular glucose levels. One of ordinary skill in the art would have had a reasonable expectation of success because Cote teaches that a method for monitoring intracellular concentration involves using different size particles (column 24 lines 62-65) and Chick also teaches that selectivity can be accomplished using molecular size (column 16 line 47). In addition, Walt teaches that there are fluorescent dyes (such as acetoxymethyl ester form of BCECF) that are cell membrane permeant, thus allowing intracellular concentrations of analytes to be measured when needed. Further evidence is provided by Applicant's disclosure

which states on page 18 line 28 of the specification, "it is well known that specific dyes bind to cellular structures and allow imaging and anatomical/histological studies of intracellular structures". In addition Chick specifically teaches that a variety of modes of placing the reagents in communication with the analytes may be used (column 16 line 37).

One of ordinary skill in the art would have been motivated to use the acetoxymethyl ester form of BCECF in the method of Chick because Walt teaches that it is a suitable form of BCECF for use as a pH indicator, which is what Chick is using BCECF for (column 14 line 63). One of ordinary skill in the art would have had a reasonable expectation of success because Walt describes how the acetoxtmethyl ester form of BCECF passively enters the cell where, once inside the cell, the lipophilic blocking groups are cleaved by non-specific esterases resulting in an increase in fluorescent intensity.

The application time for the sensor composition would clearly be a result effective variable since the penetration of the skin by the skin sensor would be required for the proper monitoring of the metabolites and analytes of an individual. The accuracy of the results of the method would indicate if the sensor composition had been applied for a sufficient amount of time. In addition, different formulations of sensor compositions would require different application times as well. According to 2144.05 of the MPEP, "Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Therefore, the selection of a specific

application time clearly would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that the accuracy of the method and the formulation of the sensor composition would be dependent upon the application time.

Therefore, the combined teachings of Chick, Cote, Walt render obvious Applicant's invention as claimed.

Claims 27, 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chick et al (US 6,040,194), Cote et al (US 6,485,703 B1) and Walt et al (US 6,377,721) as applied to claims 19, 23-26, 28, 29, 30-36, 38, 39, 40-42 above, and further in view of Heller et al (US 5,972,199).

Claims 27, 37 are drawn to the method as described above including lactate as the metabolite elected by Applicant.

Chick, Cote and Walt combined teach the method of Applicant as described above, but do not specifically include lactate as a metabolite to be measured.

Heller teaches that assay of biochemicals, such as glucose and lactate, is important in medicine, biotechnology and food processing (dairy and wine). Heller also teaches that monitoring of lactate in fluids of the human body is of relevance to diagnosis of trauma, of myocardial infarction, congestive heart failure, pulmonary edema, septicemia, hemorrhage, and others (column 1 lines 23-30).

Therefore, one of ordinary skill in the art would have been motivated to use the method of Chick to monitor levels of lactate in a patient because Heller teaches that monitoring of lactate in fluids of the human body is of relevance to diagnosis of trauma, of myocardial infarction, congestive heart failure, pulmonary edema, septicemia, hemorrhage, and others (column 1 lines 23-30). One of ordinary skill in the art would have had a reasonable expectation of success because Chick teaches that suitable analytes include inorganic or organic ions (column 5 line 15) and lactate is an ion that is found in bodily fluids.

Therefore, the combined teachings of Chick, Cote, Walt and Heller render obvious Applicant's invention as claimed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 19 and 23-42, 54-57 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 22-25, 31-50, 53 and 54 of copending Application No. 11/349,731. Although the conflicting claims are not identical, they are not patentably distinct from each other because the skin sensor composition of the co-pending application is the same as the small molecule metabolite reporters of the instant application. This is made evident by the fact that the skin sensor compositions recited in claims 24 and 53 of '731 are the same as those recited in claim 25 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura Schuberg whose telephone number is 571-272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leon B Lankford, Jr
Primary Examiner
Art Unit 1651

Laura Schuberg